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Exploring the Nutraceutical Potential of Grape Seed Extract

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Grape seed extract has important medicinal properties because of its therapeutic and nutraceutical potential. Its application as a supplement has increased over last few years. Grape seed extract contains many polyphenolic compounds such as proanthocyanidins that have positive health effects like increased athletes' performance, delayed onset of Alzheimer's disease, protection from cardiac disorders, anti-tumor proliferative and anti-inflammatory effects, lowering the peroxidation rates of LDL and many other health benefits yet to explored. Previously people consumed the seeds as a whole or grind it at home but now-a-days commercially available techniques of extraction like liquid extraction, separation with other solvents like methanol, ethyl acetate and acetone are available. Characterization of proanthocyanidins by advanced analytical techniques like High performance liquid chromatography (HPLC), Mass Spectroscopy, near infrared spectrometer (NIR) and Nuclear Magnetic resonance (NMR) have made this product a main focus for many nutraceutical industries. Recent researches in field of nutrition and herbal medicines have shown that poly phenolic compounds have numerous health benefits like cyanidins and proanthocyanidins composed of 3 monomeric units like catechin, epicatechin and epigallocatechin. Grape seed extract in the form of dietary supplements or pills is considered safe within limited doses but have shown allergic reactions for people prone to allergies. The aim of this review paper is to study the nutraceutical potential and numerous health benefits of grape seed extract in field of emerging herbal supplements and natural medicines which lowers the health risks as compared to allopathic medicines with minimum side effects.

Keywords: Essential oil, grape seed, extract, proanthocyanidins, polyphenols.

INTRODUCTION

The nutritional and medicinal properties of grapes have been known for many centuries. Egyptians and several ancient Greek philosophers consumed this fruit thousands of years ago and considered it a medicinal herb because of its healing power. They developed ointments from its sap to treat dermis and eye diseases and grape plant leaves were used to stop bleeding and to treat inflammations. Unripe grapes were used to treat cough and throat pain and dried grapes were used to treat thirst and gastrointestinal issues (Sravanthi et al., 2013). It is believed that the grape (Vitis vinifera, often known as the "Muscat of Alexandria") originated in North Africa and then spread over the Mediterranean from the port of Alexandria, Egypt, most likely during the Roman Empire. Muscat of Alexandria has many uses; it is used for dessert wine and blending in southern Europe, Africa, and South America, and as a table grape in Spain, Italy, Japan, and South America (Madbouly et al., 2025). Grapes are cultivated in various regions of the world but it is usually native to Asia, abundantly cultivated in South East Asia and Thailand. In 1600's they were brought to North America and Europe. Currently, China, Italy, France and USA are major producer of grapes. It has many varieties and different colors like green red or purple (Matthanus, 2008). There are several categories of grapes with respect to their purposes such wine grapes, table grapes, seedless, edible seed and raisin grapes. Seeds of grapes can be gathered as a byproduct from any wine producing company. Grape Seed Extract (GSE) is typically made from the seeds of red wine grapes (Gupta et al., 2020). Grapes is the best source of phenolic compounds which are present in skin and seeds. Total phenolic compounds concentration which is present in red grapes varies and mostly present in leaf, skin, stem and seeds rather than its pulp.

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According to most of the studies highest concentration of phenolic compounds is present in seeds. The concentration of these phenolic compounds varies according to region of cultivation, soil contents, climatic changes and method of cultivations, in addition to this phytochemical such as gallic acid, catechin and epicatechin known for their antioxidant properties (Novaka et al., 2008 ; Da Porto & Natolino, 2017). In 20th century after the discovery of French Paradox interest was developed in grape seed extract. According to this paradox in French population the mortality rate due to heart diseases was still low despite the consumption of high fat diet (Natella et al., 2002). Grape seed oil act as a functional ingredient and its nutrient content depends on grapes variety which usually ranges from 10-16% of the dry weight. It contains high levels of phenolic compounds, vitamin E, tannins, phytosterols, catechin, epicatechin, trans-resveratrol and carotenoids. It contains both polyunsaturated and monounsaturated fatty acids. Linoleic acid which is polyunsaturated in nature and present in abundant amount in grape seed oil where its percentage varies from 66-75% in cold compressed grape seed oil. Oleic acid also presents in grape seed oil is monounsaturated fatty acid. The high content of unsaturated compounds has several health promoting effects such as prevents thromboembolism and cardiovascular disorders, reduced serum cholesterol, dilation of blood vessels and regulation of nerves system (Garavaglia et al., 2016).

Proanthocyanidins are present in higher amounts in grapes seeds and skin. Other compounds are anthocyanins, flavanols, phenolic acids and resveratrol. Proanthocyanidins are oligomeric anthocyanins usually polymers of catechin. It is safe to consume and possesses a broad spectrum of pharmacological and nutraceutical properties. It has a powerful antioxidant potential in aqueous extract and has shown antifungal, antibacterial and antiviral properties (Hernandez-Jimenez et al., 2002).

Grapes are mostly cultivated for vine production because it has more flesh or pulp proportion as compared to seeds. Seeds usually considered as waste product in wine and juice industry and used for animal feed despite of its numerous functional and health beneficial properties. Grape seed extract is available commercially in different forms such as in liquid, tablets or capsules. Only small quantities are needed for the effect to be felt. Supplements dose ranges between 100 to 400 mg. According to some studies it has better antioxidant potential as compared to vitamin C and E (Perumalla et al., 2011).

There are several extraction techniques for the grape seed as its direct utilization is not preferred due to the bitter taste of seed. Commercially available extraction techniques include Sonication extraction, Microwave assisted extraction and Supercritical fluid extraction (Perez et al., 2005).In fact, a recent study of health promoting effect of grape seed extracts shows that it increases level of antioxidants in body. Antioxidants are the chemical substances that destroy free radicals otherwise these free radicals can damage body by altering the cell membranes, causes DNA mutations, contribute to the ageing process, a number of diseases including cancers and even cause death. Antioxidants in the Grape Seed Extract (GSE) can neutralize free radicals and to some extend reduce the damage they cause (Pastrana-Bonilla et al., 2003).

***Active Constitute of Grape Seed Extract*:** Grapes belong to *Vitaceace* family having seeds 2-4 in numbers and pyriform or ovoid in shape. Proanthocyanidin extracts obtained from grape seed are better antioxidants and inhibitors of oxidative damage to tissues than beta carotene, alpha tocopherol, beta carotene and alpha tocopherol combined effects. More than half of the procyanidins in grape seed extracts consisted of more than 5 subunits. In addition to oligomeric and polymeric proanthocyanidins several galloyl proanthocyanidins are also present which include the gallate esters of dimeric procyanidins and small amount of gallic acid (Sravanthi et al., 2013).

***Flavonoids*:** Grape seeds extracts contains flavonoids almost 5% including kaempferols-3-O-glucosides, quercetin-3-O-glucosides, quercetin and myricetin (Georgiev et al., 2014).

***Polyphenols*:** Grapes are rich source of polyphenols and 60-70% of grapes poly phenols are present in grapes seeds extracts. The grape seed polyphenols are flavan-3-ol derivatives. The compounds which are present in more amount include catechin, epicatechin, epicatechin-3-O-gallate, procyanidins dimmers, proanthocyanidins C1 and proanthocyanidins B5-32-gallate (Montealegre et al., 2006; Tarek et al., 2025). Grape seed polyphenols have a higher antioxidant activity as compared to other well-known antioxidants (such as vitamin C, vitamin E, and b-carotene). Beside their antioxidant activity, it also contains some enzymes that catalyze the release of histamine during inflammation and allergies (Gupta et al., 2020).

***Anthocyanins*:** It includes 3-glucosides, 3-acetylglucosidies, 3-coumaroylglucosides, 3-caffeoylglucoside, 5-diglucosides, 3-acetyl-5-diglucosides, 3-coumaroyl-5-diglucosides and 3-caffeoyl-5-diglucosides of cyanidins, delphinidin, peonidin, petunidin.

Stilbene derivatives: Trans-resveratrol (trans-3, 5, 40-trihydroxystilbene) studies have shown stilbenes' presence in grape seed extracts (He et al., 2010).

Table 1. Composition of Grape seed (Shinagawa et al., 2015).

Parameters	Percentage (%)
Moisture	7%
Ash	3%
Protein	11%
Fiber	35%
Fat	7-20%

Table 2. Phytochemicals present in red Grape seed extracts (Negro et al., 2003 **;** Ma and Zhang, 2017**).**

Total phenols (GAE)*	8.58g/ 100g DM
Total flavonoids (CE)**	8.41g / 100g DM
Total flavonoids (CyE)***	5.95g/100g DM

*Gallic acid equivalents; **Catechin equivalents; ***Proanthocyanins (cyanidins equivalents)

***Properties of Grape seed Proanthocyanins (GSPs)*:** Proanthocyanins belongs to the larger group of polyphenolic compounds, these compounds evolve from the plant's natural metabolic pathways of either the acetate pathway or the shikimic acid pathway. These differ in chemical structures and size owing to different monomeric units. Nonetheless, GSPs encompass various health properties (Preuss et al., 2002; Shinagawa et al., 2015).

Proanthocyanins are composed of three monomeric units of catechin, epicatechin and epigallocatechin. These vary in size from mono form to oligomeric form as monomers dimers, trimers and oligomers as large as 20 or more units. These compounds are usually water soluble except the tannins which are large condensed structures and insoluble in nature (Huang et al., 2005). These proanthocyanidins in GSE has shown a number of health benefits like cholesterol lowering effects, protective against ischemic heart diseases, cause apoptosis of cancer cells by activation of caspases and protection of normal cell in chemotherapeutic treatments (Santos-Buelga & Scalbert, 2000). Recent advances in field of nutraceuticals have shown that proanthocyanidins in grape seeds exhibit numerous benefits than once believed. There are many methods to extract and characterize grape seed extracts.

***Extraction Techniques*:** With broad range of nutraceutical action, grape seed extracts containing proanthocyanidins are attracting the attention of both pharmacists and nutraceuticals industries now-a-days. Numerous properties of phenolic compounds in GSE, where type of extraction method plays an important role, temperature and time also have great impact on the yield and quality of the nutraceutical compounds extracted. If we use efficient extraction technique it could aid in complete utilization of the active compounds in GSE. Traditional methods such as solid & liquid extraction methods require more time and large amount of solvents. In addition, large amounts of solvents cause serious environmental hazards. Latest extraction techniques have been developed as an alternative to conventional extraction methods, which need to be ventured for large scale production. GSE extraction is often done in the form of powder. The first step in the GSE extraction process is gathering grapefruit seeds, which are then cleaned, dried, and ground using a pulverizer to produce grapefruit seed powder. The extraction of active ingredients like phenolics from grapefruit seeds in high yield necessitates the optimization of several crucial factors, primarily the degree of comminution, solvent type, extraction time, extraction temperature, extraction pressure, etc., much like the extraction process for other plant polyphenol extracts (Roy et al., 2023). These techniques have to be applied to improve extraction time, amount of solvent, quantity and quality of nutraceuticals extracts.

***Liquid/liquid extraction*:** This is a widely used method of isolating proanthocyanidins from grape seeds. Water along with other solvents is most commonly used. Other methods in which methanol, ethanol and acetone used have also proven to be effective but they are not so effective as using ethyl acetate and water (Xu et al., 2010). However, water extracts are safe but other solvents must be removed from extracts even in minute amount to enhance safety status.

The initial phase started with whole grapes handpicked from a particular region and full skin intact. Skin and flesh are removed by hands and then seeds are separated. Then drying is done, if we want to store, it can be stored under standard freezing conditions until use. There is no data available which shows that whether or not freezing process damage the functional properties of the seeds (Wei et al., 2001). Grinding process does not increase or decrease the proanthocyanidins level but it can reduce the extraction time, however grinding process can increase the impurities. While it is possible to extract proanthocyanidins from grape seeds by only using ethyl acetate but it is impractical because of long rate of reaction. Combining the ethyl acetate and water directly affect the reaction rate because water increase the permeability and also increase the yield (Wei et al., 2001).

Various studies have shown that extraction of poly-phenols is maximum when system saturation is done with water. The ratio of ethyl acetate and water is 90:10. When water contraction in extraction system is below 10%, grapes seeds are not saturated and affect the optimum selectivity and yield. It is also observed that if water concentration is more than 10% it also decreases selectivity however it may increase the extraction of proanthocyanidins from grape seeds (Saucier et al., 2001). Extraction time is an important factor in extraction of proanthocyanidins from grape seeds. The maximum time for the extraction was considered to be 24 hours. It was observed that extraction increases at rapid rate up to 15 hours and after that if decreased. In most cases maximum yield obtained after 15 hours, but 15 hours is maximum to collect sizeable amount of proanthocyanidins from grape seed (Wei et al., 2001; Saucier et al., 2001).

***Separation with other solvents*:** Although ethyl acetate is ideal for the extraction but there are some other solvents (varies in polarity) that can be used to extract proanthocyanidins. If extraction of proanthocyanidins for nutraceuticals uses then ethyl acetate/water techniques is not appropriate so ethanol water extraction is used in which we use 50% ethanol and 50% water to extract polyphenols from seeds, ultra-filtration membrane system with pore size of 0.22 um used to concentrate the extract, this process does not involve any toxic material (solvent) so it is a preferred method for nutraceutical industries. For analytical purpose

purification is achieved by preparative chromatography. According to the literature it shows that ethyl acetate & water system is used as standard extraction method analytically other methods are not commonly used for extracting maximum amounts of proanthocyanidins (Nawaz et al., 2006). Other method for analytical purpose includes methanol acetone and water in different combinations and proportions. It can also be used in combination with extracting agents other than ethanol and acetate. Acetone also considered a common extracting agent. Sometimes considered best when combined with water commonly used in series with other solvents like methanol, ethanol, ethyl acetate (Labarbe et al., 1999).

***Advanced Analytical Techniques*:** Characterization of proanthocyanidins can be accomplished through different advanced analytical techniques, the five most common techniques are High Performance Liquid Chromatography (HPLC), Carbon & Hydrogen Nuclear Magnetic Resonance (NMR), Mass Spectroscopy, Infrared Spectroscopy (IR) and Gas Chromatography (GC) (Liu et al., 2012).

***High Performance Liquid Chromatography*:** It is based on non-covalent interactions of the compounds. A column is used as a stationary phase that contains a solvent which is called as mobile phase is applied to the column at constant rate. In this method the liquid sample which contains proanthocyanidin injected into column with the mobile phase at a given time. The sample through non-covalent interaction interact with both mobile and stationary phase based on present compound. Compound that has more ionic properties will react more strongly than the compound that has no ionic attributes. The interaction of compound with the phase is the basis for eluting that compound from the column. More ionic the compound more will be the retention time. A detector is attached at the end of the column to identify different compounds group and amount based on mobile phase and compound interactions. Often this detector is an UV detector set at the wavelength of 280 nm. HPLC alone is not capable of proanthocyanidins characterizations (Liu et al., 2012; Peng et al., 2001).

***Mass Spectroscopy*:** Mostly used for the composition determination and can be explained by examination of experiments that cranberries contain many polyphenols in a group that shows ornithine decarboxylase activity induced by specific pathway. By the application of spectroscopy, the proanthocyanidins responsible for this reaction were identified and further studied (Kandil et al., 2002).

***Carbon & Hydrogen NMR*:** Both carbon and hydrogen NMR are used for identification purpose. Many studies have shown the use of this advanced analytical technique for the identification of specific compound and similar group of molecules likes proanthocyanidins. It is possible to use any version of NMR without any prior isolation method (Liu et al., 2012; Stevens et al., 2022)

***Near Infrared Spectroscopy*:** It is a modern method for detection and measurement of general and complex components in both liquid and solid samples including dissolved solids, different concentrations of acid, microbial contaminations, percent contents of oils, carbohydrates, proteins and moistures. It can also determine concentrations of different compounds. The advantage to rapid computer technology that utilize complex mathematical computations, including Fourier transformation allows relationship between variation of multiple parameters and NIR spectra, the NIRs allows sampling through glass and plastic making it more efficient process. When combined with proven chemical and analytical processes, results can be translated into reliable NIR spectrometric calculations. This can potentially measure various phytochemical components in small amounts of sample (Liu et al., 2012).

***Supplementations of GSE and Limitations*:** GSE available as dietary supplement in form of capsules or liquid extracts. Choose products standardized to 40-80% proanthocyanidin or 95% Oligomeric Proanthocyanidins (OPC) content. In 1997 the grape seed extract was 7th most popular herbal supplement that was sold in USA by food, drug and mass market retailers (Blumenthal, 1998). Suggested dosage for the grape seed OPC is 50-150 mg per day. In some studies, grape seed extract dosage varies from 200-400mg per day while in other studies dose rate of 1mg per body weight per day are recommended (Yamakoshi et al. 2002).

Grape seed extracts are generally recognized as safe by Food and Drug Administration. It was added to United States food databases and sold as food supplement in market. Bentivegna and Whitney demonstrated in their studies that no adverse side effects was seen in rats' model at Higher level of 1.78 g per day per body weight which is considered as safe upper limits of grape seed extract supplementation (Bentivegna et al., 2002). According to another clinical trial there was no adverse clinical or physiological effecting individuals taking 200-400mg of supplementation of GSE. Likewise, no adverse changes were seen in urinary laboratory sample of these individuals. Likewise, in an animal study there is no noticeable signs of toxicity (Feei-Ma et al., 2017).

According to a research grape seed extract may cause interactions or some side effects for some people. In an 8 weeks-controlled trial Caucasian men were given grape seed extract which have shown that GSE are safe to use. Grape seed extract may interact with other medications and may cause symptoms like nausea, vomiting, diarrhea, dizziness, headache and itchy skin. Generally grape seed extract is considered as safe natural supplement but during preparation there is chances of mixing of certain chemicals which on contrary serve as toxic and leads to certain side effects but there are no proven documentation regarding adverse gastrointestinal symptoms or any other allergies while using grape seed extract supplements (Berry et al., 2015). Earlier, a study, demonstrated no observed adverse effect level of grape seed OPCs was 1400-1500mg per kg per day which is equal

to 90-100 mg grape seed extract for an average 150 pounds person (Hosseini et al., 2001).

Nutraceutical Potential

Antioxidant Role: Grape seed extract has antioxidant activity and destroy free radicals by neutralizing them. Proanthocyanidines, not only scavenge free radicals but also inhibit xanthine oxidase activity to a greater extend, the enzyme which stimulates the oxy-radical cascade in a study, when mice fed with low concentrations about 2mg/day of proanthocyanidins the polyunsaturated fatty acid peroxidation reduced in them. Some *in vitro* studies have shown that grape seed Proanthocyanidin extract (GSPE) in concentrations of 50mg/L prevents the effects of free radicals because its free radical scavenging effect is better than other antioxidants like vitamins C and E. Moreover, GSPE in concentrations of 100mg/kg, as compared to other antioxidants can protect oxidative damage. In addition to these properties, procyanidin B4, epicatechin, and gallic acid in low concentrations of 10Ïmol/L, 25 mol/L protect against cellular damage and DNA damage (Feei-Ma et al., 2017).

Table 3. The antioxidant capacity in different parts of grape (extracts) and product (Xia et al. 2010).

Resources	FRAP	DPPH
Grape pomace	-	0.20 g/L (EC50)
Grape seed	-	>663 umol TE/g
Deffated grape seed	21.6 mol TE/100 g	-
Whole seed	58.04 mol TE/100g	-
Grape seed	-	16.8 to 92 mmol TE/g
Grape skin	-	15.7 to 113.3 mmol TE/g
Grape juice	32 mmol fe2+/L	15mmol TE/L

Grape seeds proanthocyanidin extract modify the antioxidant systems, it suggests that grape seed proanthocyanidins can improve the cellular redox reactions via glutathione synthesis pathways [35]. Another study reported that proanthocyanidins provides protection against the ethanol induced toxicity in brain tissues of rats. Supplementation of 50 mg/kg and 100 mg/kg grape seeds proanthocyanidins extract in rodent named hamsters reduced the formation of foam cells by 50% and 63% (Guo et al., 2007).

***Anti-Platelet Activity*:** Grape seed extracts also have anti-platelet activity. In a study it is reported that grape seed extracts in dose of 5 to 50 g/ml showed that platelet aggregation, adhesiveness and production of super oxide anion have been reduced. The researchers also demonstrated that grape seed extract is more effective than the resveratrol in the reducing platelet aggregation (Olas et al., 2008).

***Anti-Cholesterol Effects*:** Grape seed extract supplements also protect against oxidative damage induced by Methotrexate (MTX) that is a cytotoxic chemotherapeutic agent. In a 12 weeks dose of supplements which contains 0, 200 and 400 mg grape seed extract given to 61 healthy individuals who have LDL cholesterol level of 100 to 180 mg/dl. A study shows that effect of supplementation in 300 mg dose on high fat meal in 8 male adults. Grape seed extracts increase the plasma antioxidant concentrations which reduce postprandial oxidative stress and prevented the increase of lipid hydroperoxides (Seigers et al., 2016). Likewise, it also increased the resistance to oxidative modification of LDL cholesterol. Other studies have shown that the poly-phenolic compounds in grape seed extracts activate serum paraoxonase (PON) and this enzyme inhibits the postprandial increase of lipid peroxides. This enzyme is a high-density lipoprotein (HDL) that hydrolyzes lipoprotein peroxides and inhibits LDL oxidation (Natella et al., 2002).

***Protects Cardiovascular System*:** One of the main issues brought on by today's unhealthy lifestyle is cardiovascular disease (CVD), which is the leading cause of death globally. In general, cardiovascular disease (CVD) is the state in which the heart's and blood vessels' functions change, potentially resulting in cardiac arrest, heart attack, chest pain, etc. A vital component of CVD prevention is lifestyle. The risk of CVD is decreased by a healthy diet high in natural fruits and vegetables, frequent exercise, etc. Risk factors for the development of atherosclerosis and CVD include diabetes mellitus, high blood pressure, and dyslipidemias, all of which can be decreased by altering one's lifestyle (Masana et al., 2017). The miraculous properties of grape seeds are well known due to its beneficial effect on heart health. Grape seed extract can treat hypertension, prevent the damaging of blood vessels and the deleterious oxidation of LDL cholesterol that is the very first step on a way to heart attack or stroke. In past some years, grape seed extract has become a preferred and beneficial herbal medicine for a variety of health benefits, from hypertension to preventing cancer. High concentrations of (oligomeric proanthocyanidins) OPC in grape seed extract have numerous benefits and nutraceutical potential. In a clinical study conducted in Italy, subjects with pre and mild high blood pressure issues divided into three groups, two receiving grape seed extract, at lower and higher doses, and one with a dietary modification and lifestyle changes, as a control group. At the end of that 4-month trial, both grape seed extract groups showed an improvement from hypertension levels with more efficiency at high doses (300mg). In fact, hypertension normalized in 93 percent of subjects in the higher dosage group. The blood vessel dilating properties of grape seed extracts is also known, blood vessels dilate rather than restrict, blood moves with less force, reducing blood pressure. This study showed that grape seed procyanthocyanidins increase nitric oxide (NO) release and also cyclic GMP levels. Nitric oxide is a molecule which activates in bloodstream for a few seconds at a time and considered a free-radical but actually has beneficial effects for blood pressure, signals for the opening of blood vessels and

arteries. Cyclic GMP (cGMP) have relaxation effects on smooth muscles, including blood vessels. Oxidative stress (lipid peroxidation products, lipid hydroperoxides in plasma and MDA-LDL) and hyperlipemia in postprandial stage known as risk factor for development of atherosclerosis, according to researchers it can be reduced by an appropriate dose of grape seed extract. In rat models, grape seed extract can protect against oxidative damage (Sano et al., 2007).

***Anti-Inflammatory Effects*:** A study shows the effects of proanthocyanidin from grape seeds on the inflammatory mediators in mice fed on high fat foods, in a study on rats, those who were fed on a high fat foods supplemented with proanthocyanidins from grape seeds in concentration of 345 mg/kg of feed for a duration of 19 week had a lower plasma C reactive protein (CRP) level than rat with high fat intakes only, this study shown that the reduction in plasma levels of CRP is related to a down regulation of gene expression of CPR in the liver and white adipose tissue (Terra et al., 2009). The author also reported a reduction in the expression of the pro inflammatory cytokine tumor necrosis factor alpha (TNF) and interleukin 6 (IL-6) in White Adipose tissues (WAT) of rats (Terra et al., 2009).

Those rats who were fed on grape seed procyanidin extracts have shown reduction in body weight and plasma systemic markers of TNF and CRP. Procyanidin extracts also increase adiponectin expression and decreased interleukin-6 and also linked to a reduced expression of epidermal growth factor modulator containing mucin like receptor. EMR1 it is a specific marker of macrophage F4/80 has shown a reduced macrophage infiltration of White Adipose tissues (WAT). Therefore, the daily consumption of food containing procyanidins can protects against low grade inflammation related to obesity characterized by accumulation of macrophages. In addition, grape seed procyanidins stimulates the glucose transporter 4 movements in plasma membrane. Procyanidins possesses insulin like effects in insulin sensitive cells. So, all these findings suggested that procyanidins and proanthocyanidins in grape seeds reduce the risk of diseases associated to obesity and high fat diets (Feei-Ma et al., 2017; Terra et al., 2011).

***Anti-Microbial Potential*:** Grape seed extracts are rich sources of polyphenols. Grape seeds extract also shown antimicrobial properties. Grape seed extracts which is de-fatted were shown to exhibit antimicrobial effects against species of *Bacillus cereus, Bacillus subtilis, Staphylococcus aureus, Bacillus coagulans, Escherichia coli*, and *Pseudomonas aeruginosa*. These polyphenols inhibit the activities of Gram positive and Gram negative bacteria at 850–1000 ppm and 1250–1500 ppm, respectively. A study has shown that grape seed extracts exhibited antibacterial effect to *Micrococcus luteus Aspergillus niger*, and *Fusarium oxysporum*, with a diameter of the inhibition growth zone ranged from 15–20 mm (Ghouila et al., 2017). Future studies should be based on assessing the grape seed extracts for compounds naturally impart antimicrobial activities. Previously, research reported that muscadine grape seed extracts were effective in inhibiting *H. pylori in vitro* [45, 29]. This showed that although muscadine grape seed extracts had the highest total phenolic content (646 mg GAE/g dry weight) than skin extracts (135 mg GAE/g dry weight), the skin extracts had a higher efficacy than seed extracts against *H. pylori.* That's why it is concluded that the anti *H. pylori* activity might be influenced by the type and content of phenolics. However, *H. pylori* infection is linked with several gastric and duodenal diseases such as gastric ulcers. When resveratrol is administered topically to healthy skin, it promotes the formation of cathelicidin, which prevents Staphylococcal aureus from growing and causes antimicrobial peptide (Park et al., 2013).

Anti-diabetic Effects: It is reported that grape seed powder extract (GSPE) is effective in treatment of diabetic nephropathy, but there is little data about changes in functional proteins. After effects of GSPE induced therapy in diabetic rats, only 9 renal proteins returned to normal level. So it concluded that these proteins are involved in oxidative stress, glycosylation damage, and amino acid metabolism. GPSE in 25 mg doses also prevents glycation linked cardiac damage in diabetic rats. According to a study, OPC in grape seed extract interact with insulin receptors, activate it and by auto-phosphorylation it can improve the insulin uptake by receptors (Montagut et al., 2010).

Anti-Tumor Activity: GSP supplements have also shown anti-tumor properties. Numerous researchers performed on human colorectal cancers, head and neck cells related carcinoma, and prostate cancer. Therefore, it is suggested that the grape seed extracts supplementation are effective anti-tumor therapy in clinical set up (Feei-Ma et al., 2017).

Bladder Cancer: The nutraceutical potential of grape seed proanthocyanidin extract (GSPE) on cell proliferation and programmed cell death in human bladder cancer BIU87 cells was demonstrated in a study. The findings showed that GSPE induce cell cycle arrest and inhibits cell proliferation in BIU87cells, and its effect was related with down regulation of cyclinD1, CDK (Gordillo, 2009).Grape seed extract (GSE) protects against bladder cancer and its associated mechanism of action in two different bladder cancer cells T24 and HTB9 was evaluated. Result showed that GSE induced oxidative stress causes a strong apoptosis in cancer cells of bladder. Grape seed extract (GSE) protects against azoxymethane (AOM) induced colon colitis via epigenetic micro RNA (miRNA) regulation. The results have shown that inhibition of azoxymethane induced colon cancer by dietary GSE is mediated by the induction of apoptosis which is linked with alterations in messenger RNA (mRNA) and cytokine expressions as well as β-catenin signaling pathways (Gordillo, 2009; Masoudi et al., 2017).

Oral Cancer: The nutraceutical potential of grape seed procyanidin (GSP) on anti-proliferative effects linked to p53

functional levels of oral squamous cell carcinoma (OSCC) was scrutinize. The results clearly shown that GSP may play a role as a chemo preventive or therapeutic agent because grape seed extracts having anti-proliferative effects on the most commonly existing type of oral carcinoma called oral squamous cell carcinoma. Result showed that cranberry and grape seed extracts can prevent oral cancer proliferation and also regulates apoptosis for these cells (Lin, 2012).

The cytotoxic effects and the mechanism of apoptosis induced by grape seed extract (GSE) in oral squamous cell carcinoma (KB cells) showed apoptotic potential of GSE, as significant inhibition of cell growth and confirmed it as workable in a dose and time dependent manner without causing damage to non-cancerous cells. Grape seed extracts were scrutinized in yeast cells issues in their antioxidant system. The grape seed extract performs a pro-oxidant role *in vivo* in accordance with antioxidant deficiencies at cellular levels and shows cytotoxic activities in PC3 and HepG2 2.2.15 cell lines, but no antiviral against HBV. Anti-proliferative properties of GSE have been noticeable in many carcinomas but rare in oral cancer. Different concentrations of grape seed extract have a different anti-proliferation functioning against oral cancers because of contrasting apoptosis, oxidative stress and DNA damage (Masoudi et al., 2017).

Breast Cancer: The powerful biological effect of grape seed extract (GSE) on the highly metastatic MDA-MB231 breast cancer cell was scrutinized. The results make GSE a miraculous agent against cancer metastasis. The effect of grape seed extract (GSE) on breast cancer cell MCF-7 for expression of gene and proliferation of cancer cells was observed. Result showed that by stopping the cell cycle in S period, the proliferation of breast cancer cells MCF-7 can be stopped. The biological activity of grape seed proanthocyanidin extract (GSPE) in inhibition of cellular carcinogenesis was induced by a long-time exposure to environmental carcinomas. A lab model with biological and molecular target end points confirmed the value of GSPE preventing the human breast cell carcinogenesis evoked by numerous time exposure to low doses of several environmental carcinogens (Masoudi et al., 2017).

Hepatoprotective Effects: According to a study the pre-exposure of grape seed extract for 3-7 days in concentration of 100 mg/kg, followed by acetaminophen (400 and 500 mg.) more importantly rarely acetaminophen induced hepatic DNA damage, apoptotic and necrotic cell death of hepatic cells and this reversed the effects of acetaminophen induced changes in expression in rats (Hani et al., 2017). In another study, grape seed extract of the 50 mg/kg a day oral administration for 28 days prevents the liver cirrhosis followed by bile duct ligation in mice. Another study has also shown the protective effect of red grape seeds against liver cytotoxicity in rats' model (Geogiev et al., 2014).

5.13. ***Other Health Benefits:*** A research on mice mandibles in its growth period suggested that dietary supplementation with GSPE may increase bone quality and strength of the mandibles. Grape skin extract in concentration of 200mg/kg/day also proved protective effect against preeclampsia in an experimental rat, it is a condition in which nitric oxide production reduced and oxidative stress increased. Conclusively, experimental preeclampsia, the GSE plays an important role owing to endothelium dependent vasodilation and antioxidant actions (Robinson et al., 2012). A study reported that grape seed extracts minimized brain weight losses ranging from 20% in vehicle pups to 3% in treated pups. Brain damage is demonstrated by lose of brain weight with hypoxic ischemic brain injury. In addition to this it also improved the histopathologic brain score in cortex, hippocampus, and thalamus. The supplementation with grape seed extracts used to inhibit lipid peroxidation and decrease the chances of hypoxic ischemic brain injury (Souad et al., 2017).

***Effects of Grape Seed Extract Supplementation on Exercise Performance in Athletes*:** Grape seed extract has another potential endogenous aid resourceful of increasing exercise performance. GSE is a major source of polyphenols and contains biologically active compounds such as monomers of catechin, epicatechin, and gallic acid esters. These extract lowers the blood pressure and linked with improved endothelial functions. GSE has also been reported to lower the mild hypertension in healthy human subjects. A laboratory experiment evaluated the effects of different concentration of GSE supplementation on cardiac responses to sub-maximal dynamic exercise in pre hypertensive subjects. In comparison to placebo conditions, exercising BP, vascular conductance, and heart workout (heart rate x systolic BP & RPP) were reduced and cardiac output increased. In addition to this endothelial functioning in the sinew of skeletal muscle was improved. The GSE enhance the cardiac output and vascular conductance also shows that oxygen delivery also enhanced. Furthermore, the enhancement in endothelial functioning also increased capacity for vasodilation it is an outcome that increase the oxygen delivery to skeletal muscle. Conclusively, lower blood pressure response indicates reduced load on heart. So, these findings showed that GSE supplementation act as endogenous aid that prolongs the onset of muscle and physical activity during any athletic workout or exercise (Jong et al., 2005).

Cardiovascular effects of GSE involves the mechanism of increase in nitric oxide production and also increase its bioavailability (Reid, 2016). This mechanism can occur *via* the nitrate nitrite NO pathway or activation of the endothelial NO synthase pathway. When bioavailability of nitric oxide increased it leads vascular smooth muscle's protein activation e.g., guanylate cyclase, cyclic GMP, and protein kinase G phosphorylation which cause relaxation. Relaxation of vascular smooth muscle increase vasodilation, in turn it increases the blood flow to contracting skeletal muscle. Potential therapeutic and nutraceutical effects of GSE on

athletes engaged in intensive physical activities and endurance trainings are currently unknown. Furthermore, future findings mainly focus on acute and chronic effects of GSE on exercise and athletic performance is a new era of investigation (Jong et al., 2005; Reid, 2016).

Conclusion: The therapeutic and medicinal properties of grape seed extract is well known as it contains many biologically active ingredients like catechin, epicatechin, gallic acid, flavonoids and proanthocyanidins. Seeds contain highest proportion of these beneficial compounds specially a high content of proanthocyanidins. New extraction techniques are becoming popular as compared to conventional techniques as it can yield maximum number of polyphenolic compounds from the grape seed and GSE supplements becoming nutraceutically important now a days because of its numerous health benefits. Procyanidins and proanthocyanidins have many active roles in body like scavenging free radicals, anti-inflammatory and anti-bacterial properties etc. Likewise, it is also important in treating cardiac diseases, diabetic nephropathy, hepatic cirrhosis and protective against certain type of cancers and malignancy like breast, colon or oral cancers. It can also increase the heart output, oxygen delivery and reducing muscle fatigue in endurance training and exercise performances. There is not known toxicity by oral administration of grape seed extract but it can cause allergic reactions in some people prone to allergies. Further researcher is required to access the maximum levels that cause toxicity. Grape seed extract approved as generally recognized as safe GRAS by food and drug administration in the ranges of 200 to 400 mg. Further researches and investigation are required to find out the mode of action of grape seed extracts on disease prognosis and improved exercise outcomes and how we can obtain its optimum yield without any toxic residue left for use in nutraceutical industry. So, this step is still a challenge in nutraceutical era.

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